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(54) Process for Producing Substituted-Phenethylamine
Derivatives

(72) Fujikura, Takashi , Japan
Niigata, Kunihiro , Japan

(73) Yamanouchi Pharmaceutical Co. Ltd. , Japan

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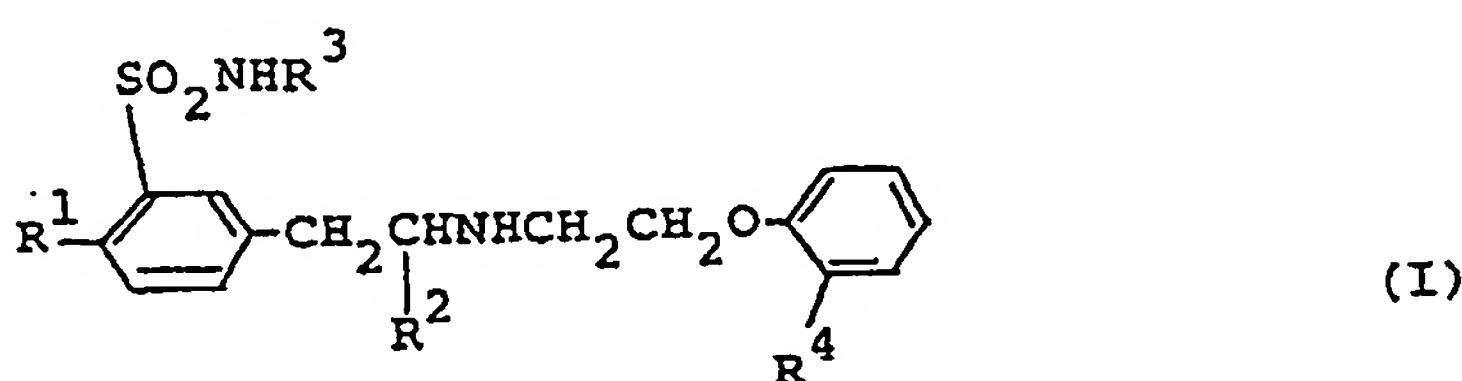
SPECIFICATION

Title of the invention:

A novel process for producing substituted phenethylamine derivatives

Detailed explanation of the invention:

This invention relates to a process for producing a compound of the following formula (I) and a salt thereof



wherein R¹ represents a lower alkyl group, a lower alkoxy group, or a hydroxyl group; R² represents a hydrogen atom, or a lower alkyl group; R³ represents a hydrogen atom or a lower alkyl group; and R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, or a hydroxyl group (hereinafter, these means the same significances).

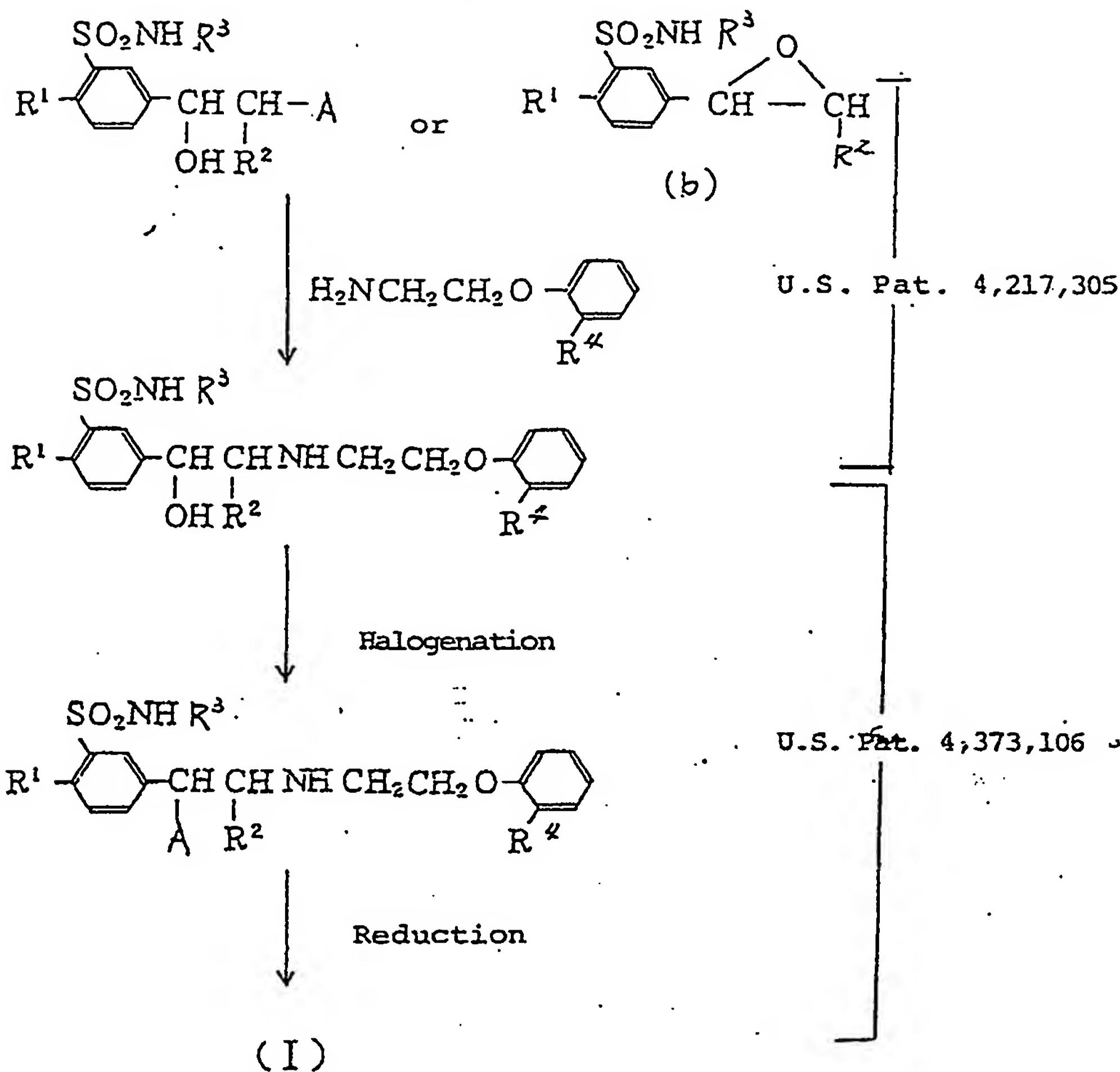
U.S. Patent 4,373,106 discloses that the above formula (I) compounds exhibit α -adrenergic blocking action and are useful as an antihypertensive agent and an agent for the treatment of congestive heart failure.

So far, the formula (I) compounds have been produced by a process disclosed in U.S. Patent No. 4,217,305 or 4,373,106. This prior art process is as follows:



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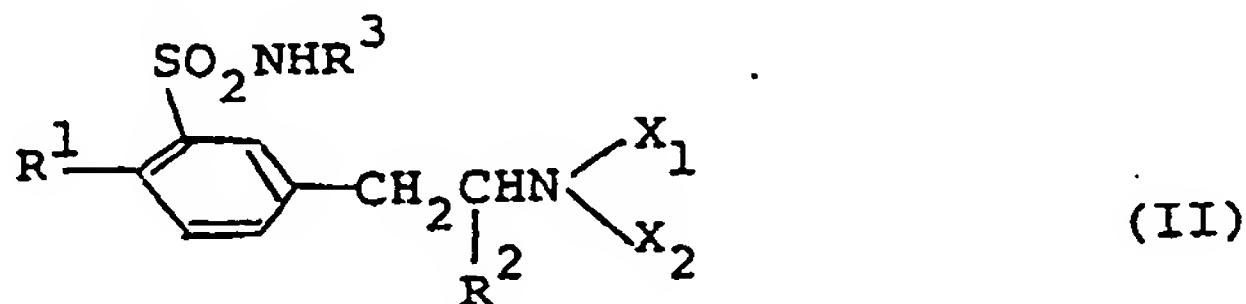
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(In the above formulae, A represents a halogen atom, and R¹, R², R³ and R⁴ are as defined above.)

An object of the invention of this application is to provide a novel process for producing the formula (I) compounds which process is easy and suitable for industrial production of the compounds (I).

That is, this invention relates to a process for producing a compound of the formula (I) or a salt thereof which comprises reacting a compound of the formula



(wherein R¹, R², and R³ are as defined above; and X₁ and X₂ represent a hydrogen atom or a protective group for an amino group) or a salt thereof with a substituted phenoxy compound



[wherein R⁴ is as defined above; and Y represents an aldehyde group which may be protected, or -CH₂-Z- (Z represents a removing group) and then, if Y is an aldehyde group which may be protected, reducing the formed compound.

The compounds (I) contain an asymmetric carbon atom if R² is a lower alkyl group, and the aimed compounds (I) of the process of this invention include the racemic compounds thereof, a mixture of the racemic compounds and each optically active substance. Each optically active substance or the racemic compounds of the compounds (I) can be produced by using an optically active or racemic compound of the starting material (II).

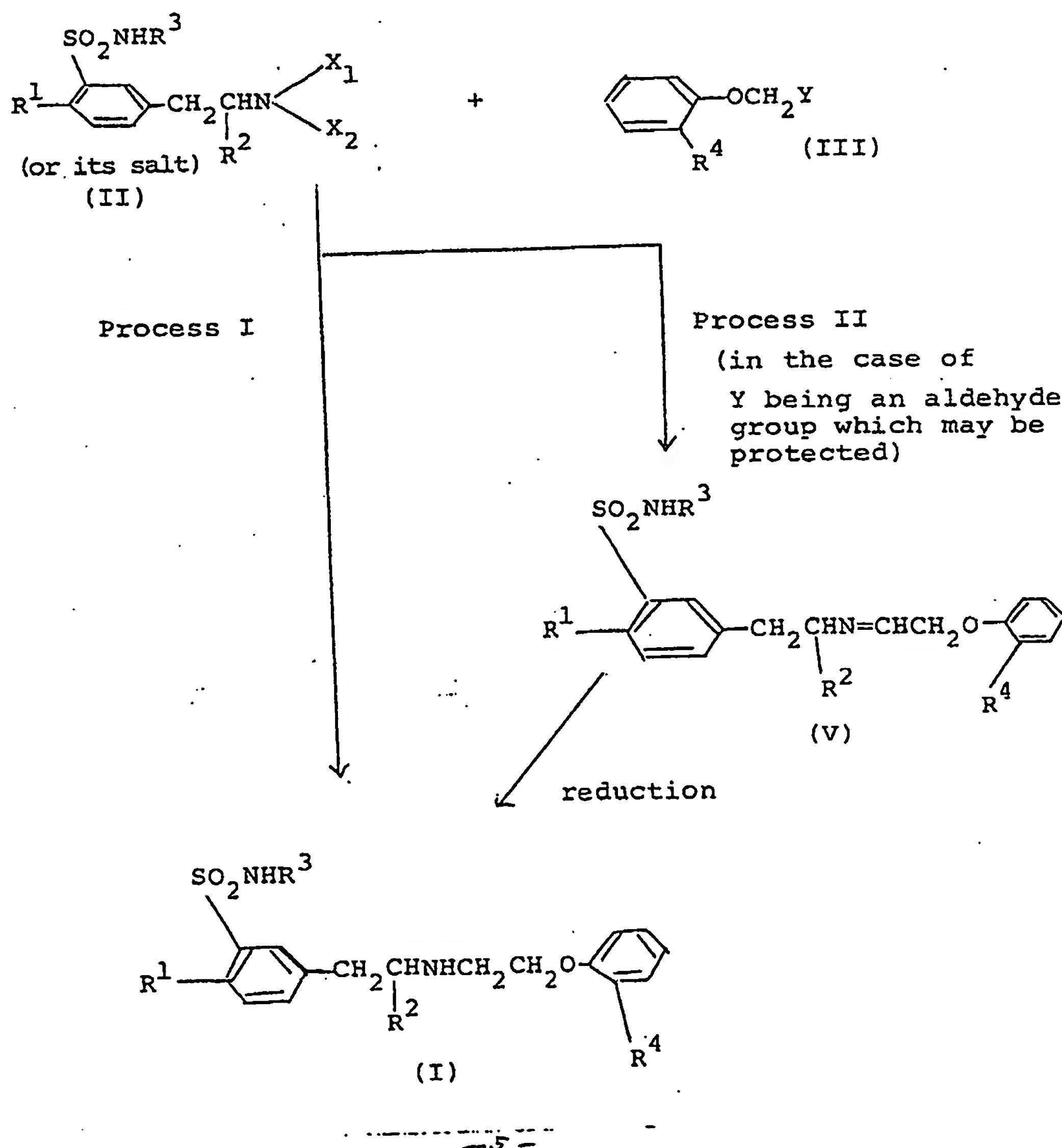
The term "lower" used in the above formula means a straight or branched chain having 1 to 5 carbon atoms. Therefore, for example, a lower alkyl group includes methyl group, ethyl group, propyl group, butyl group, pentyl group, isobutyl group, etc., and a lower alkoxy group includes methoxy group, ethoxy group, propoxy group, butoxy group, etc. The term "halogen" in the formula means chlorine, bromine, iodine or fluorine. As a protective group for an amino group for X_1 or X_2 , there are, for example, trityl, substituted-trityl, benzyl, substituted-trityl, benzyl, substituted-benzyl, benzyloxymethyl, substituted-benzyloxy, trimethylsilyl, methoxymethyl, etc.; as a protective group for an aldehyde group for Y, there are, for example, dialkylacetals (e.g., dimethylacetale, diethylacetale, etc.), ring structure acetals (e.g., ethyleneacetale, etc.), acylales (e.g., diacetyl, etc.), which protective groups do not affect the reactions and can be easily released. As a removing group which Z means, there are, for example, a halogen atom, or an organic sulfonic acid residue such as tosyl, methanesulfonyl,

The compounds (I) or the starting compounds (II) can form salts thereof, e.g. a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid or phosphoric acid, or with an organic acid such as formic acid, acetic acid, citric acid, succinic acid, fumaric acid, maleic acid, tartaric acid, methanesulfonic acid, ethanesulfonic acid, etc. These salts can be produced by an ordinary manner for producing such salts.

The processes of the invention are further described in more detail.

Firstly, a phenethylamine compound (II) or its salt is reacted with an reactive equivalent amount of a substituted phenoxy compound (III) in an organic solvent suitable for the reaction (Process I), and then, if Y is an aldehyde group which may be protected, the formed compound is subjected to a reducing reaction (Process II).

These processes are schematically shown below.



Process I:

This process (that is, the reaction of a phenethylamine compound (II) or its salt with a substituted phenoxy compound (III)) can be performed in a solvent (which is inert to the reaction) such as alcohols (e.g., methanol, ethanol, iso-propanol, etc.) ethers (e.g., dioxane, tetrahydrofuran), acetonitrile, dimethyl-formamide, dimethylsulfoxide, etc. An equimolar or excess amount of the compounds is used for the reaction. It may be preferred to use an equimolar amount of Compounds if there exist inorganic base (for example, potassium carbonate, sodium carbonate, sodium hydrogen carbonate, etc.) or an organic base (for example, triethylamine, pyridine, picoline, N,N-dimethylaniline, N-methylmorpholine, etc.). In the case of the compound (II) being used, it may be preferred to perform the reactions in the presence of an inorganic or organic base. The reaction temperature or time may be changed suitably, considering the kind of Compound (II) or (III), or of solvent. The reaction is preferably performed in usual at room temperature or under heating such as under reflux.

Process II:

The reaction of a phenethylamine compound (II) or its salt with a substituted phenoxy compound in case of Y being an aldehyde group which may be protected, is usually performed in a solvent which is inert to the reaction and can solubilize the reaction compounds (e.g., alcohols such as methanol, ethanol, iso-propanol; ethers such as tetrahydrofuran, dioxane; acetonitrile, dimethyl-formamide, dimethylsulfoxide) at room temperature or under heating.

The reaction can be finished in about 1 hour. The formed compound (IV) (in the reaction solution or after isolating) is then reduced. In this process, an acetal compound may be used instead of the formula (III) compound (in this case, the acetal compound is firstly hydrolyzed by using an inorganic acid (e.g., hydrochloric acid), an organic acid (e.g., acetic acid, formic acid, toluenesulfonic acid, methanesulfonic acid), an organic acid salt (e.g., pyridine-toluenesulfonic acid salt), etc., and then, is subjected to the following reaction). The reduction can be accomplished in alcohols (e.g., methanol, ethanol, isopropanol) or ethers (e.g., dioxane, tetrahydrofuran by adopting catalytic reduction using platinum oxide, palladium catalyst, Raney nickel,* or by using metal hydride such as sodium borohydride, sodium borocyanohydride, lithium borohydride, lithium aluminum hydride, etc.

*Trade Mark

The desired compounds of this invention thus prepared is obtained as free base or its salt. The free base compound may be subjected to a salt forming reaction by a usual method, and the salt may be isolated and purified by usual manner. The isolation and purification of the compounds can be accomplished by usual chemical procedures such as filtration, extraction, recrystallization, reprecipitation, various chromatographies, etc.

(Effects of the invention)

In the case of the prior art methods for producing the compounds of this invention, there are needed many steps of reaction, and so there is a difficulty in the prior art methods for its industrial application. In the case of this invention, there is needed only an extremely fewer steps than the prior art methods, since the reaction procedures are simple; and the desired compounds can be obtained in high yield. Accordingly, the method of this invention is very suitable for the industrial application.

Further, the reactions of this invention never accompany racemisation. Hence, each optical isomer of the formula (I) compound can be selectively produced by using corresponding optical isomer of the starting material (II) which is

easily produced.

In order to explain the invention in more detail, there are set out below Reference Examples and Examples. The formula (III) compounds which are starting materials for the processes of this invention, are novel compounds, and Reference Examples below show the production thereof. Further, optical isomers of the phenethylamine derivatives of the formula (II) and their production are shown in Reference Examples 2 and 3.

Reference Example 1.

— Sodium hydride (in oil, 60%; 4.6g) was stirred in dry dimethylformamide (100 ml), and after adding slowly there-to 13.8 g of o-ethoxyphenol, the resultant mixture was stirred under heating at 60°C for 1 hour. Then, under ice-cooling, 19.7 g of bromoacetaldehyde diethyl acetal was added dropwise to the reaction mixture over a period of 1 hour. The reaction mixture was stirred at room temperature overnight, was heated while stirring at 60°C for 2 hours, and then was poured into 500 ml of ice-water. After extracting with ethyl acetate, the extract was washed with water, and dried over anhydrous sodium sulfate. The solvents were distilled away to give oily residue. The residue was distilled under reduced pressure to give oily material of 2-(o-ethoxyphenoxy)acetaldehyde diethyl acetal (12 g).

Boiling point: 113-116°C (0.5 mmHg)

¹H-NMR (CDCl₃) δ: 1.24 (6H, t, J=7 Hz, -CH₂CH₃ × 2), 1.42 (3H, t, J=7 Hz, -CH₂CH₃), 3.4~3.9 (4H, m, -OCH₂CH₃ × 2), 3.9~4.2 (4H, m, -OCH₂CH₃, -OCH₂CH<), 4.86 (1H, t, J=5 Hz, -OCH₂CH<), 6.88 (4H, s, aromatic ring)

Reference Example 2 (Preparation of R(-) compound)

a) In 6 ml of pyridine was dissolved 1.5 g of R(-)-2-(p-methoxyphenyl)-1-methylethylamine ([α]_D²³: -30.1° (c=1.2, methanol)), and after adding thereto 3 ml of acetic anhydride, the mixture was allowed to stand at room temperature for 1 hour. After distilling off the solvent, the residue was extracted with ethyl acetate. The ethyl acetate extract was washed with water, and dried over anhydrous sodium sulfate; and the solvent was distilled off and the crude crystals formed were recrystallized from a mixture of n-hexane and benzene to provide 1.8 g of (R)(+)-N-acetyl-2-(p-methoxyphenyl)-1-methylethylamine.

Melting point: 92-93°C

Elemental analysis for C₁₂H₁₇NO₂:

C(%)	H(%)	N(%)
Calcd.: 69.54	8.27	6.76
Found: 69.41	8.19	6.66

[α]_D²⁴: 14.8° (c=1.09, methanol)

b) In 60 g of chlorosulfonic acid was added 6 g of (R) (+)-N-acetyl-2-(p-methoxyphenyl)-1-methylethylamine, under cooling at 0 to -10°C. The mixture was stirred for 1 hour at 0 to 5°C, and the reaction solution was poured into 600 g of ice-water. The oily material precipitated was extracted with ethyl acetate, and the ethyl acetate extract was washed by a saturated aqueous sodium hydrogen carbonate solution and dried over anhydrous sodium sulfate. After distilling off the solvent, the formed residue (without purification) was dissolved in 120 ml of tetrahydrofuran. After adding dropwise thereto 180 ml of a concentrated aqueous ammonia solution, the mixture was stirred for 1 hour at room temperature. The crystals precipitated were collected by filtration, washed with water, and recrystallized from methanol to provide 6 g of (R) (+)-N-acetyl-5-[(2-amino-2-methyl)-ethyl]-2-methoxybenzenesulfonamide; another name: R (+)-5-[2-acetylamino)propyl]-2-methoxybenzenesulfonamide.

Melting point: 197-198°C

Elemental analysis for C₁₂H₁₈N₂O₄S:

	(C%)	H(%)	N(%)
Calcd.:	50.34	6.34	9.78
Found:	50.28	6.41	9.69

$[\alpha]_D^{24}: 14.7^\circ$ (c=1.0, methanol)



c) 5 g of (R) (+)-N-acetyl-5-[(2-amino-2-methyl)ethyl]-2-methoxybenzenesulfonamide was dissolved in 125 ml of 5% hydrochloric acid, and the solution was refluxed under heating for 16 hours. After distilling off the solvent, the crude crystals formed were recrystallized from isopropanol to provide 4.5 g of (R) (-)-5-[(2-amino-2-methyl)ethyl]-2-methoxybenzenesulfonamide; namely, R(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide (HCl salt).

Melting point: 273-277°C (decomposition)

Elemental analysis for C₁₀H₁₇ClN₂O₃S:

	C(%)	H(%)	N(%)
Calcd.:	42.78	6.10	9.98
Found:	42.68	6.00	9.93

$[\alpha]_D^{24} = -6.3^\circ$ (c=1.03, methanol)

Reference Example 3 (Preparation of S(+)
compound)

a) By following the same procedure as in Reference Example 2(a), (S) (-)-N-acetyl-2-(p-methoxyphenyl)-1-methylethylamine was obtained by using S(+) -2-(p-methoxyphenyl)-1-methylethylamine.

Melting point: 94-96°C

Elemental analysis for C₁₂H₁₇NO₂:

	C(%)	H(%)	N(%)
Calcd.:	69.54	8.27	6.76
Found:	69.47	8.31	6.64

$[\alpha]_D^{24} = -15.3^\circ$ (c=1.25, methanol)

X

b) By following the same procedure as in Reference Example 2(b), (S) (-)-N-acetyl-5-[(2-amino-2-methyl)-ethyl]-2-methoxybenzenesulfonamide (another name: S(-)-5-[2-(acetylamino)propyl]-2-methoxybenzenesulfonamide) was obtained by using (S) (-)-N-acetyl-2-(p-methoxyphenyl)-1-methylethylamine as the starting material.

Melting point: 196-198°C

Elemental analysis for $C_{12}H_{18}N_2O_4S$:

	C(%)	H(%)	N(%)
Calcd.:	50.34	6.34	9.78
Found:	50.31	6.24	9.73

$[\alpha]_D^{24}:-14.2^\circ$ (c=1.01, methanol)

c) By following the same procedure as in Reference Ex. 2(c), (S) (+)-5-[(2-amino-2-methyl)ethyl]-2-methoxybenzenesulfonamide was obtained by using (S) (-)-N-acetyl-5-[(2-amino-2-methyl)ethyl]-2-methoxybenzenesulfonamide as the starting material.

Melting point: 273-276°C (decomposition)

Elemental analysis for $C_{10}H_{17}ClN_2O_3S$:

	C(%)	H(%)	N(%)
Calcd.:	42.78	6.10	9.98
Found:	42.65	6.03	9.89

$[\alpha]_D^{24}$: 6.0° (c=1.01, methanol)

X

Example 1

2.8 g of 2-(o-ethoxyphenoxy)acetaldehyde diethyl acetal was dissolved in 20 ml of acetone, and after adding thereto 3 ml of 6N-hydrochloric acid, the mixture was stirred for 1.5 hour at room temperature. The solvent was distilled away and after adding water to the residue, the precipitated oily material was extracted with ether. The ether extract was washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled away to give oily residue. The residue was dissolved in 100 ml of methanol and after adding thereto R(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide (2.4 g), the mixture was refluxed under heating for 1 hour. After cooling, 0.25 g of platinum oxide catalyst was added, and the reaction mixture was subjected to reduction reaction by a usual manner. The catalyst was removed by filtration and after acidifying the filtrate with HCl-ethanol, the solvent was distilled away. The residue was recrystallized from methanol to give R(-)-5-[2-[(2-(o-ethoxyphenoxy)ethyl)amino]propyl]-2-methoxybenzenesulfonamide HCl salt.

Melting point 228-230°C $[\alpha]_D^{24} -4.1^\circ$ (methanol)

Example 2

By following the same procedure as in Example 1, by using S(+) - 5-(2-aminopropyl)-2-methoxybenzenesulfonamide (instead of R(-) - 5-(2-aminopropyl)-2-methoxybenzenesulfonamide), S(+) - 5-[2-[(2-(o-ethoxyphenoxy)-ethyl)amino]propyl]-2-methoxybenzenesulfonamide HCl salt.

Melting point: 228-230°C $[\alpha]_D^{24} +4.1^\circ$ (methanol)

Example 3

By following the same procedure as in Example 1, by using racemic compound of 5-(2-aminopropyl)-2-methoxybenzenesulfonamide (instead of R(-) - 5-(2-aminopropyl)-2-methoxybenzenesulfonamide), racemic compound of 5-[2-[(2-(o-ethoxyphenoxy)ethyl)amino]propyl]-2-methoxybenzenesulfonamide HCl salt.

Melting point: 254-256°C

Example 4

2.8 g of 2-(o-ethoxyphenoxy)acetaldehyde diethyl acetal was dissolved in 20 ml of acetone, and after adding thereto 3 ml of 6N-hydrochloric acid, the resultant mixture was stirred at room temperature for 1.5 hour. The solvent was distilled away, and after adding water to the residue, the precipitated oily material was extracted with ether. The ether extract was washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled away to give oily residue. The residue was dissolved in 100 ml of methanol and after adding thereto 2.4 g of R(-) - 5-(2-aminopropyl)-

-2-methoxybenzenesulfonamide, the mixture was refluxed under heating for 1 hour. Then, sodium borohydride (0.42 g) was added to the mixture at 5-10°C over a period of 1 hour, the mixture was allowed to stand overnight. The solvent was distilled away, and the residue was extracted with ethyl acetate. The extract was washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled away, and the residue was treated with HCl-ethanol, and recrystallized from methanol to give R(-)-5-[2-[(2-(o-ethoxyphenoxy)ethyl)amino]propyl]-2-methoxybenzenesulfonamide HCl salt.

Melting point: 228-230°C

$[\alpha]_D^{24} +4.1^\circ$ (methanol)

Example 5

By following the same procedure as in Example 4, by using S(+)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide (instead of R(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide), S(+)-5-[2-[(2-(o-ethoxyphenoxy)ethyl)propyl]-2-methoxybenzenesulfonamide HCl salt.

Melting point: 228-230°C

$[\alpha]_D^{24} +4.1^\circ$ (methanol)

Example 6

By following the same procedure as in Example 4, by using racemic compound of 5-(2-aminopropyl)-2-methoxybenzenesulfonamide (instead of R(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide), racemic compound of 5-[2-[(2-(o-ethoxyphenoxy)ethyl)propyl]-2-methoxybenzenesulfonamide HCl salt. Melting point: 155-156°C.



Example 7

In 120 ml of ethanol were dissolved 2.4 g of (R) (-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide and 1.2 g of 2-(o-ethoxyphenoxy)ethyl bromide, and the mixture was refluxed for 16 hours under heating. The solvent was distilled away, and after alkalizing the residue by the addition of 10% sodium hydroxide, and the oily material precipitated was extracted with ethyl acetate. The extract solution was washed with a saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was distilled away, and the residue was subjected to column chromatography. The product was eluted with CHCl_3 -methanol (9:5) to provide 1.5 g of the crude crystals of (R) (-)-5-[2-[(2-(o-ethoxyphenoxy)-ethyl)amino]-2-methylethyl]-2-methoxybenzenesulfonamide, which was treated with HCl-ethanol to give a hydrochloric acid salt of (R) (-)-5-[2-[(2-(o-ethoxyphenoxy)ethyl)-amino]propyl]-2-methoxybenzenesulfonamide.

Melting point: 228-230 °C

Elemental analysis for $\text{C}_{20}\text{H}_{29}\text{ClN}_2\text{O}_5\text{S}$:

	C (%)	H (%)	N (%)
Calcd.:	53.99	6.57	6.30
Found:	53.90	6.64	6.27

$[\alpha]_D^{24} = -4.0^\circ$ (c=0.35, methanol)

Example 8

By following the same procedure as in Example 7 (S) (+)-5-[2-[(2-(o-ethoxyphenoxy)ethyl]amino]-propyl]-2-methoxybenzenesulfonamide HCl salt was obtained by using (S) (+)-5-[(2-aminopropyl)-2-methoxybenzenesulfonamide as the starting material.

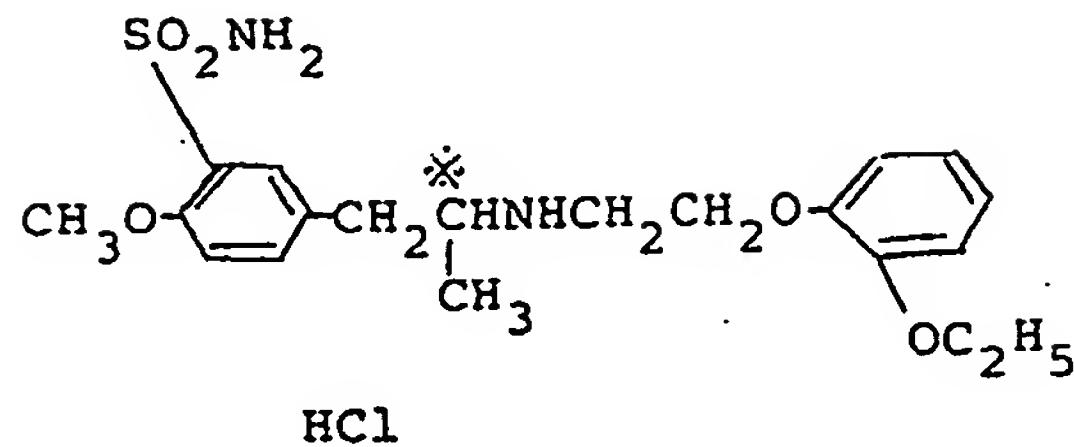
Melting point: 228-230°C (methanol)

Elemental analysis for $C_{20}H_{29}ClN_2O_5S$:

	C (%)	H (%)	N (%)
Calcd.:	53.99	6.57	6.30
Found:	53.92	6.57	6.45

$[\alpha]_D^{24} : 4.2^\circ$ (c=0.36, methanol)

Example 9



1) In 40 ml of water was dissolved R(-)-5-(2-amino-propyl)-2-methoxybenzenesulfonamide HCl salt (4 g) by heating, and after adding thereto 14 ml of a saturated aqueous potassium carbonate solution, the mixture was stirred at 5°C for 2 hours. The precipitated crystals were collected by filtration, and the crystals obtained were recrystallized from ethanol to give 2.6 g of R(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide.

Melting point: 166-167°C

$[\alpha]_D^{23} -17.3^\circ$ (c=1.07, methanol)

2) In 5 ml of N,N-dimethylformamide were dissolved 976 mg of R(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide and 245 mg of 2-(o-ethoxyphenoxy)ethyl bromide, and after heating the solution at 60°C for 5-7 hours, the solvent was distilled away. To the residue was added 28 ml of water, and the mixture was refluxed under heating for 30 minutes. The mixture was stirred at 5°C for 1 hour, and the crystals precipitated during the stirring were collected by filtration. The crystals collected were recrystallized from iso-propanol to give 320 mg of R(-)-5-[2-[(2-(o-ethoxyphenoxy)ethyl)amino]-

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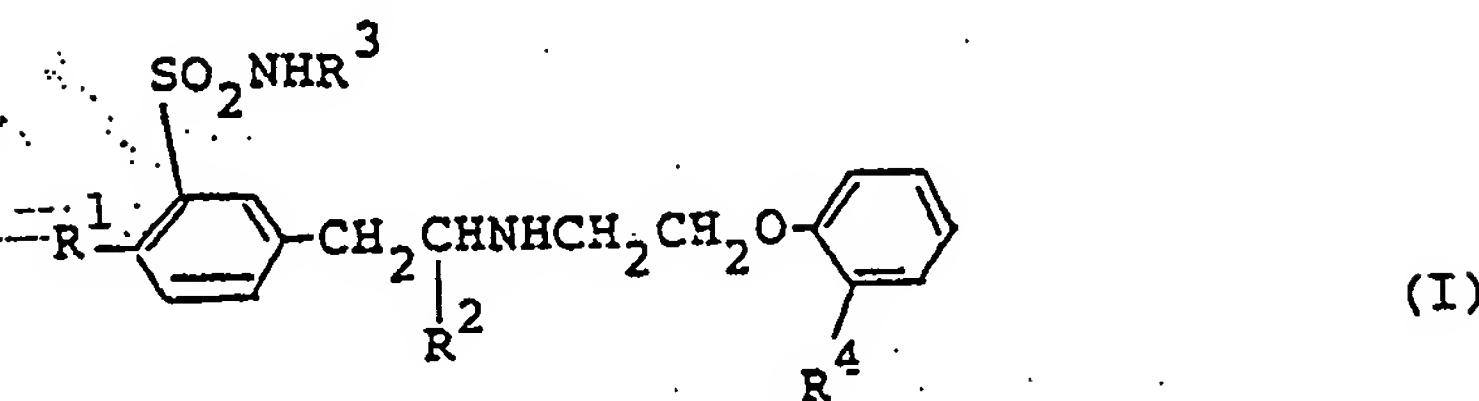
Elemental analysis for $C_{20}H_{29}ClN_2O_5S$

	C(%)	H(%)	N(%)
Calcd.:	53.98	6.57	6.30
Found:	53.90	6.55	6.29

$[\alpha]_D^{23} 4.2^\circ$ (c=0.36, methanol)

Claim(s):

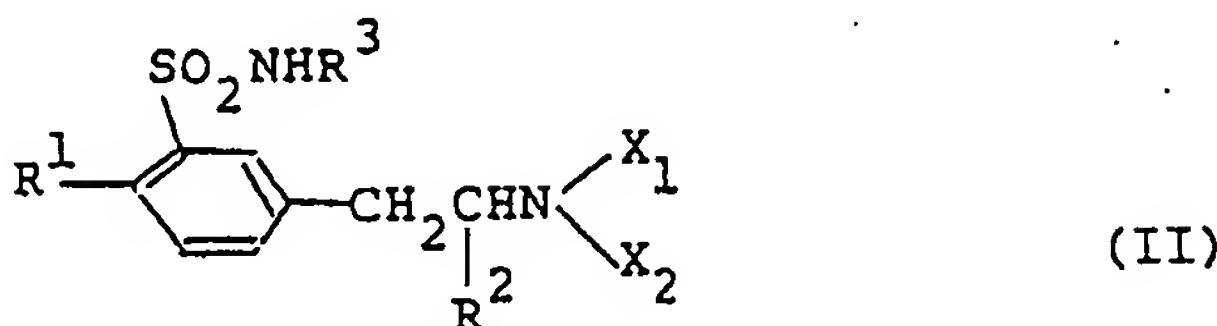
1. A process for producing a compound of the following general formula (I) or a salt thereof



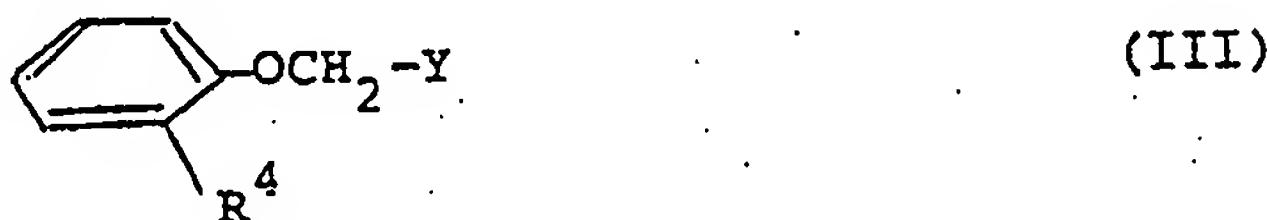
wherein R¹ represents a lower alkyl group, a lower alkoxy group, or a hydroxyl group; R² represents a hydrogen atom, or a lower alkyl group; R³ represents a hydrogen atom or a lower alkyl group; and R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, or a hydroxyl group,

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which comprises reacting a compound of the following formula (II)



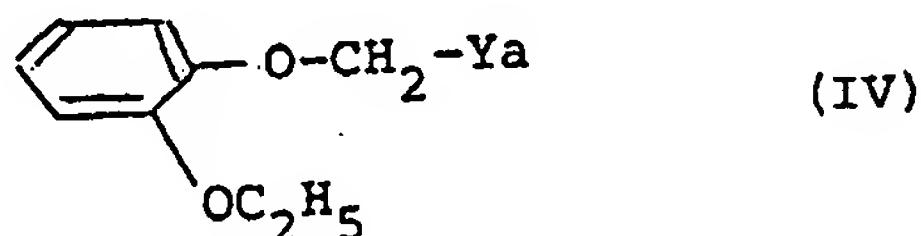
(wherein R¹, R², and R³ are as defined above; and X₁ and X₂ represent a hydrogen atom or a protective group for an amino group) or a salt thereof with a substituted phenoxy compound



(wherein R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group; and Y represents an aldehyde group which may be protected, or -CH₂-Z- (Z represents a removing group) and then, if Y is an aldehyde group which may be protected, reducing the formed compound.

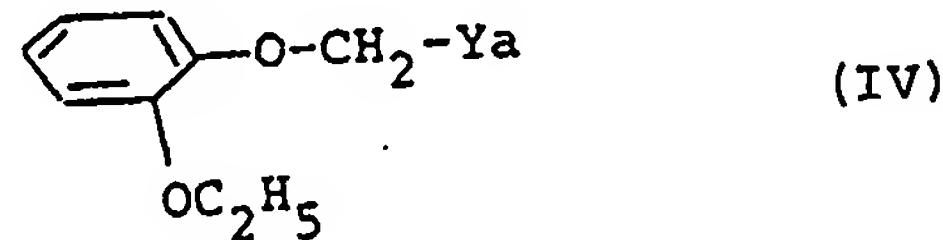
2. A process according to claim 1 wherein R^1 is a lower alkoxy group, R^2 is a lower alkyl group, R^3 is a hydrogen atom, and R^4 is a lower alkoxy group.

3. A process according to claim 1 or 2 for producing 5-[2-[(2-(o-ethoxyphenoxy)ethyl)amino]propyl]-2-methoxybenzenesulfonamide or its salt which comprises reacting 5-(2-aminopropyl) — 2-methoxybenzenesulfonamide or its salt with a substituted phenoxy compound of the formula



(wherein Ya represents a halogenomethyl group or an aldehyde group which may be protected), and then, if Ya represents an aldehyde group which may be protected, reducing the formed compound.

4. A process according to claim 1 or 2 for producing R-(-)-5-[2-[(2-(o-ethoxyphenoxy)ethyl)amino]propyl]-2-methoxybenzenesulfonamide or its salt which comprises reacting R-(-)-5-(2-aminopropyl) — 2-methoxybenzenesulfonamide or its salt with a phenoxy compound of the formula



(wherein Ya represents a halogenomethyl group or an aldehyde group which may be protected), and then, if Ya

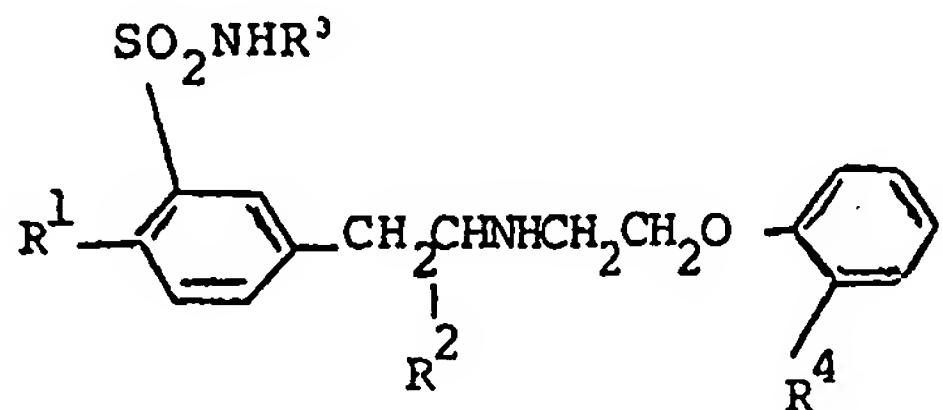
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represents an aldehyde group which may be protected, reducing the formed compound.

5. A process according to claim 1 for producing each optically active compound of the formula (I) compound which comprises reacting each corresponding optically active compound of the formula (II) compound with the formula (III) compound.



A novel process is disclosed for the production of substituted phenethylamine derivatives of the formula:



wherein R¹ represents a lower alkyl group, a lower alkoxy group, or a hydroxyl group; R² represents a hydrogen atom, or a lower alkyl group; R³ represents a hydrogen atom or a lower alkyl group; and R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, or a hydroxyl group. These compounds exhibit α -adrenergic blocking action and are useful as antihypertensive agents and agents for the treatment of congestive heart failure.

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